REMARKS

This Amendment is being submitted in conjunction with Applicant's Request for continued Examination, and in response to the Final Official Action dated 18March 2009. Claims 29, 31, and 33-35 are herein canceled (claims 1, 4, 7, 8 and 10-25 were previously canceled), claims 26-28, 30 and 32 are amended, and new claims 36-40 are added. Thus, claims 26-28, 30 and 32-40 remain pending in this application.

Applicant acknowledges denial of its Petition to Reinstate its priority claim as a continuation-in-part (CIP) of prior-filed PCT application PCT/IL2002/000051 (Pub. No. WO/2002/056823), and said priority claim is herein removed from the specification.

The Examiner objected to claims 29, 31, 33 and 35 under 37 CFR 1.75c as failing to limit the subject matter of the parent claims. According to the Examiner, claims 29, 31, 33 and 35 recite inherent properties of the disclosed compounds and hence impose no additional limitations. Claims 29, 31, 33 and 35 are herein canceled.

Claims 26 and 34-35 were rejected under 35 U.S.C. § 102(a) as being anticipated by the inventor's earlier PCT application (WO 02/056823). Applicant respectfully traverses. In WO 02/056823, Hoffman discloses the use of a pharmaceutically effective amount of an E-increasing agent to retard the proliferation of a tumor and/or cause regression of a tumor. Decreasing the ratio of $[GSH]^2/[GSSG]$ increases the redox state of a cell and results in a decrease or cessation of cell proliferation. WO 02/056823 suggests that "E-increasing agent is preferably administered in an amount of from about 0.1 to about 50 mg/Kg body weight per day, preferably from about 10 to about 45 mg/Kg body weight per day, most preferably from about 20 to about 40 mg/Kg body weight per day. Thus an adult dosage of E-increasing agents may optionally be as much as about 2

grams per day or more." WO 02/056823 does not teach or suggest how many days or how frequently per day. Indeed, there is no teaching or suggestion of any particular protocol or regimen. In contrast, the present application specifically teaches that efficacy requires maintaining the raised E/dephosphorylated state of RB *continuously* for a complete cell cycle (15-75 hours), in effect, to mimic in vitro conditions. A model of the normal and cancer cell cycles is summarized in Scheme 1 of the present specification. This maintenance requirement is reflected in claim 26, which requires "*said pharmaceutically effective dosage of said drug further comprising a calibrated administration frequency to continuously maintain said decreased* $[GSH]^2/[GSSG]$ *ratio (a.k.a. "E ratio") in the malignant cells and consequently continuously maintain said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours in order to span at least one cell cycle.*" The requirement for a calibrated administration frequency for continuous maintenance of the E ratio over at least a cell cycle is essential, and is not obvious because in vivo treatment generally entails intermittent administration of the agent or agents. [See the attached Declaration of Arnold Hoffman]. Without guidance as to frequency of administration or duration of treatment, *continuous maintenance* over at least a cell cycle is not inherent. If the frequency of administration is too low the E-increasing agent disappears before the next administration, the E will decrease back towards its initial lower value, below -210 mV, phosphorylating the RB, promoting cell proliferation, and nullifying the therapy. For example, if a combination of agents raise and maintain the high E/dephosphorylated state of the pRB for 12 hours, but the administration frequency is once every 24 hours, then for several hours prior to the next

administration the E will drop back toward its initial value/RB will become phosphorylated. This promotes cell proliferation and nullifies effectiveness. On the other hand, an excessively high frequency of administration can result in an accumulation of the E-increasing agent, raising the E beyond – 180 mV, harming the normal cells. In sum, a frequency of administration for a few hours longer or shorter than required will render the treatment either ineffective or toxic, generating disappointing in vivo results. In addition, inasmuch as the treatment prevents all cell proliferation, it prevents healing/replacement of normal cells. Consequently, cells with short lifetimes, for example blood cells, may die and not be replenished during an excessively long duration of the treatment. The depletion of these cells may threaten the viability of the treated subject. The present application establishes the requirement of the drug to *continuously maintain said decreased* $[GSH]^2/[GSSG]$ *ratio in the malignant cells and consequently continuously maintain said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours in order to span at least one cell cycle*", and then proceeds to provides ample guidance for adjusting the frequency of administration to accomplish this. Present claim 26 specifically requires *continuously maintaining said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours in order to span at least one cell cycle*, and is therefore not anticipated by WO 02/056823.

In addition, claim 26 is herein amended to further distinguish WO 02/056823. Not only does the present disclosure describe maintenance of the dephosphorylated state of RB in cancer cells for between 15 to 75 hours, but it also teaches how to do it when administered intermittently to a subject. It teaches the use of a combination of agents,

some of which raise E/dephosphorylate pRB, and others that maintain the high E between administration periods. Specifically, BSO and BCNU effectively deactivate the gamma-GCS and GR enzymes, respectively, for about 15+/- 5 hours, delaying any decrease in E/phosphorylation of RB. As disclosed at [para 0064] of the published specification, by adding a second agent that irreversibly inhibits glutathione reductase (GR) the GSSG cannot be reduced back to GSH. E will remain high until there is more de novo synthesis of GR. The present application teaches how this phenomena can be exploited for a redox therapy for cancer; i.e., raise the E/dephosphorylate the pRB with E-increasing agents and maintain the raised E/ dephosphorylated state of RB by using these enzyme deactivating agents. Claim 26 is herein amended to reflect this uniquely synergistic mechanism explicitly, now requiring a combination of at least one E-increasing agent from the group of disulfram and curcumin, and at least one enzyme deactivating agent from the group of BCNU and BSO, constituting the "drug" cited in the claim. Applicant's WO application does not teach or suggest raising the E/dephosphorylating RB with E-increasing agents and continuously maintaining the raised E/ dephosphorylated state of RB at all, let alone by any synergistic combination of both: 1) a E-indecreasing agent (disulfram and/or curcumin); plus 2) an enzyme deactivating agent (BCNU and/or BSO), that in combination,) may not be synergistic in vitro, but in vivo, are synergistic.[1]

Therefore, this claim limitation is essential, yet it is absent in Applicant's PCT Application, and consequently claim 26 is patentably distinguished. Claims 34 and

[1] It is also noteworthy that Applicants PCT Application incorrectly teaches that the treatment will only be selective if the E of the normal cells is not high enough to dephosphorylate the RB. The subject application discloses that the Redox Therapy is selective even if the E of the both the normal as well as the cancer cells is high enough to dephosphorylate the RB.

35 are canceled. New claims 36-40 impose further limitations on the specific combination of agents, including the four-agent combination (disulfram and curcumin and BCNU and BSO) in claim 39, and the exclusive four agent combination in claim 40, neither of which WO 02/056823 teaches or suggests.

Claims 26 and 28-29 were also rejected under 35 USC § 102 (b) as being anticipated by Marikovsky (U.S. Patent 6,288,110 – Pharmaceutical compositions comprising disulfiram). Marikovsky teaches that administering DSF once per day will inhibit angiogenesis (growth of new capillary blood vessels), with the intention of treating angiogenesis-dependent disorders. Since Marikovky teaches only that DSF inhibits angiogenesis, one would not be led from his teaching to consider the redox therapy taught in the subject patent with its essential emphasis on the frequency of administration necessary for elevating E and continuously maintaining it high from between 15-75 hours. In addition, Marikovsky does not teach or suggest raising the E/dephosphorylating the RB with E-increasing agents and continuously maintaining the raised E/ dephosphorylated state of pRB at all, let alone by any synergistic combination of both 1) an E-increasing agent (disulfram and/or curcumin); plus 2) an enzyme deactivating agent (BCNU and/or BSO). Since claim 26 as amended recites both aforesaid requirements, claim 26 is patentably distinguished over Marikovsky. Claim 28 depends from claim 26 and further limits the combination specifically to curcumin and BSO, and is therefore further distinguished. Claim 29 is canceled.

Claims 26 and 30-31 are rejected under 35 USC § 102 (b) as being anticipated by Sharma et al. (clinical Cancer Research, July 2001, vol. 7, pages 1894-1900 -

Pharmacodynamic and Pharmacokinetic Study of Oral Curcuma Extract in Patients with Colorectal Cancer). Sharma et al. (2001) administered curcumin to patients with colorectal cancer and concluded that the doses they administered were safe. Sharma et al. did not show that the curcumin actually helped the patients or shrunk the cancer. They noted that the "Mechanisms by which curcumin prevents cancer are thought to involve up-regulation of carcinogen-detoxifying enzymes, such as GSTs." The regimen comprised the administration of curcumin once daily for 4 months. There is no teaching or suggestion of a particular dosage frequency or parameter, and as described above choosing the correct dosage frequency is essential in the redox therapy as recited in claim 26 (as amended). Dosing with curcumin once per day for 4 months in no way anticipates the teaching of the subject patent to maintain E above the threshold for up to 75 hours. Moreover, one would not be led from Sharma's method of daily dosing to the more frequent dosing that may be required to continuously maintain E above the threshold even if his method had shown any efficacy as a treatment for cancer, which it did not. [See the attached Declaration of Arnold Hoffman]. Therefore, Sharma et al. do not teach or suggest raising the E/dephosphorylate pRB with E-increasing agents and maintaining the raised E/ dephosphorylated state of pRB at all, let alone by any synergistic combination of both 1) a E-increasing agent (disulfram and/or curcumin); plus 2) an enzyme deactivating agent (BCNU and/or BSO). Since claim 26 as amended recites both aforesaid requirements, claim 26 is patentably distinguished over Sharma et al.

Claims 26 and 32-33 were rejected under 35 USC §102 (b) as being anticipated by Johnson et al. (new prior art) (Neurosurgery, 1987, vol. 20, no. 4, pages 577-583).

Johnson et al. administered BCNU relying on its DNA damaging ability to kill cancer cells. The patients were reported to have been treated at 6-week intervals, again without any indication that frequency of dosage is an important parameter. There is no obvious extension from the treatment reported by Johnson et al. to the frequency of more than once per day of the redox therapy of the subject patent. The teaching of the subject patent and the treatment of Johnson et al. rely on very different mechanisms, and it would be expected that the frequencies of dosage would be necessarily different. One could not be led to the dosage regimen of the subject patent from that of Johnson et al. [See attached Declaration of Arnold Hoffman]. Therefore, Johnson et al. does not anticipate claim 26. Moreover, Johnson et al. does not teach or suggest a synergistic combination of both 1) an E-increasing agent (disulfram and/or curcumin); plus 2) an enzyme deactivating agent (BCNU and/or BSO). Since claim 26 as amended recites both aforesaid requirements, claim 26 is patentably distinguished over Johnson et al.

Claims 26 and 34-35 are rejected under 35 USC §102(b) as being anticipated by Bailey et al. (J. Natl. Cancer Inst., 1997, vol. 89, no. 23, pages 1789-1796). Bailey et al '97 administered BSO continuously for up to 72 hours. However, they did it in conjunction with melphalan chemotherapy with the intention of lowering the GSH concentration in order to prevent the GSH from limiting the effectiveness of the chemotherapeutic agent. Bailey et al. intended and expected that *lowering the GSH concen*tration would help melphalan chemotherapy. Although the administration of BSO did indeed lower the GSH concentration, the explicit relationship of $[GSH]^2/[GSSG]$ to E , and the requirement that E has to be raised high enough to dephosphorylate RB , is not disclosed.

Since claim 26 specifically requires administration of a "drug to cause a decrease in the $[GSH]^2/[GSSG]$ ratio in the malignant cancer cells of said tumor" to dephosphorylate the RB, claim 26 is not anticipated by Bailey et al.

Moreover, Bailey et al. does not teach or suggest a synergistic combination of both 1) a E-increasing agent (disulfram and/or curcumin); plus 2) an enzyme deactivating agent (BCNU and/or BSO). Since claim 26 as amended recites both aforesaid requirements, claim 26 is patentably distinguished. Claims 34-35 are canceled.

In addition, in contrast to Bailey et al., the amended claims of the subject patent deal with intermittent admission of the agents constituting the drug and the protocol required to duplicate in vivo, in vitro conditions. Proper continuous administration of a single E-increasing agent may be able to approximate in vitro conditions.

Claims 26-29 and 34-35 were also rejected under 35 U.S.C. 103 (a) as being unpatentable over Cen et al. (Molecular Cancer Therapeutics, January 2002, vol. 1, pages 197-204). Cen et al. explore the effect of disulfiram (DSF) or BSO on apoptosis of melanoma cells in vitro, and concludes only that DSF-induced apoptosis is redox related but involves a different mechanism from BSO-induced apoptosis in tumor cells. However, again the subject patent teaches the use of adding enzyme deactivating agents (BCNU and/or BSO) to the E-increasing agents (disulfram and/or curcumin), to retard the decrease in E and extend the dephosphorylated state of the RB until the next administration of the agents. Cen et al. do not do not teach or suggest in vivo raising the E/dephosphorylate pRB with E-increasing agents (disulfram and/or curcumin) and maintaining the raised E/ dephosphorylated state of pRB with an enzyme deactivating agent (BCNU and/or BSO) to continuously maintain the dephosphorylated state

of RB (high E) from between 15-75 hours. Since claim 26 as amended specifically recited the aforesaid requirements, and Cen et al. was not aware of the above, it is not obvious to coordinate the method and frequency of administration with the nature and concentration of the agents as claimed, and claim 26 is patentably distinguished. [See the attached Declaration of Arnold Hoffman.] Claims 27-28 impose further limitations on the specific combination of agents (disulfram and curcumin and BCNU and BSO) neither of which Cen et al. teaches or suggests.

Claims 26-27 and 32-35 are also rejected under 35 U.S.C. 103 (a) as being unpatentable over Ali-Osman (Mol. Pharm., 1996, vol. 49, pages 1012-1020). However, Ali-Osman merely suggests that BCNU mitigates the cytotoxicity of BSO. Even if this would obviate the combination of BSO and BCNU, Ali-Osman still does not do not teach or suggest in vivo raising the E/dephosphorylate pRB with E-increasing agents (disulfram and/or curcumin) and maintaining the raised E/ dephosphorylated state of pRB with an enzyme deactivating agent (BCNU and/or BSO) to continuously maintain the dephosphorylated state of RB (high E) from 15-75 hours. [See the attached Declaration of Arnold Hoffman.] Claim 26 is patentably distinguished.

Claims 26-29 and 32-35 are rejected under 35 U.S.C. 103 (a) as being unpatentable over U.S. Patent No. 6,589,987 to Kennedy (Method treating cancer using tetraethyl thiuram disulfide) in view of Nagendra et al. (Alcohol, 1994, vol. 11, pages 7-10), Huang et al. (The FASEB Journal, 2001, vol. 15, pages 19-21; published online 11/09/2000), Ali-Osman et al. (Mol. Pharm., 1996, vol. 49, pages 1012-1020), and Hoffman et al. (J. Theor. Biol., 2001, vol. 211, pages 403-407). This is a piecemeal combination of prior art that ignores the unique type of in vivo synergistic effect of

Applicant's specific combination of agents and specific regimen. [See attached Declaration of Arnold Hoffman].

There are hundreds of agents that have been documented to have some anticancer effect. The Examiner's position seems to be that it would be obvious to combine any agents that have already been mentioned in the literature as having some anticancer effect under some circumstances. This view presumes that one skilled in the art would try any subset or combination of such agents as a therapy. This overlooks the reality that particular agents work together to provide synergistic effects. Conventional practice is to first screen potential anti-cancer agents by evaluating in vitro effectiveness. Agents that are effective are then evaluated in vivo, by administering these agents intermittently, to tumor bearing animals, and measuring changes in the tumor volume. Any in vitro evaluation of DSF by itself can be very highly effective inasmuch as there is no need to deal with the body's self-regulatory function, and so, for in vivo testing there is no need to combine any other agents. There is no inherent motivation to combine the conclusions of any in vitro analysis of single agents. Moreover, the prior art is entirely unaware of the need to calibrate the Administration Frequency to the effective duration of the dephosphorylated state of RB / high E. For example, given the teachings of the subject patent application, it can be calculated that for a tumor cell cycle of about 24 hours, and an effective half-life of the multi-agent drug of about 12 hours, administration frequency correlates to cell density approximately as follows:

Administration Frequency	**approximate % Increase in cell density / 24 hours[2]**
1. every 24 hours	40
2. every 18 hours	20
3. every 12 hours	death of most cells

Thus, the subject application teaches and demonstrates that, at most, (1) slows down rate of cancer growth and (3) is significantly effective. Effectiveness requires a calibration of the Administration Frequency with the value of the Duration of Dephosphorylated RB. None of the cited references teach or suggest in vivo calibration by raising the E/dephosphorylate pRB with E-increasing agents (disulfram and/or curcumin) and maintaining the raised E/ dephosphorylated state of pRB with an enzyme deactivating agent (BCNU and/or BSO) to continuously maintain the dephosphorylated state of RB (high E) from 15-75 hours. Consequently, claim 26 is patentably distinguished.

Finally the Examiner is rejecting claims 30-31 under 35 U.S.C. 103 (a) as being unpatentable over U.S. Patent No. 6,589,987 to Kennedy in view of Nagendra et al., Huang et al., Ali-Osman et al., and Hoffman et al. and further in view of Ramachandran et al. (Breast Cancer Research and Treatment, 1999, vol. 54, pages 269-278). According to the Examiner, Ramachandran et al. adds curcumin into the mix of the other individually taught agents suggested in the other individual references. Again, this presumes some inherent motivation to try any subset or combination of agents as a therapy. As explained above in detail, no such motivation exists in vitro, and in any case

[2] The in vivo experimental data disclosed in the subject patent showed that daily systemic administration gave a weak (i.e. non-random) but insignificant effect, whereas administration by direct injection into the tumor every 12 hours was highly effective, consistent with the Table.

the viewpoint ignores the unique synergistic effect of Applicant's specific combination of agents and specific regimen. From the point of view of the prior art, the experimental result in accordance with the present application's ideal in vivo conditions associated with direct administration of agents every 12 hours into the tumor (i.e significant shrinkage if not elimination of the tumor within 3 days) was entirely unexpected. [See attached Declaration of Arnold Hoffman]. Consequently, it is believed that all pending claims 26-28, 30 and 32 are allowable.

New claims 36-40 impose further limitations on the specific combination of agents, including the four-agent combination (disulfram and curcumin and BCNU and BSO) in claim 39, and the exclusive four agent combination in claim 40, and new claims 36-40 should also be allowable. Accordingly, this application is now in proper condition, and a Notice of Allowance is respectfully requested.

Respectfully submitted,

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